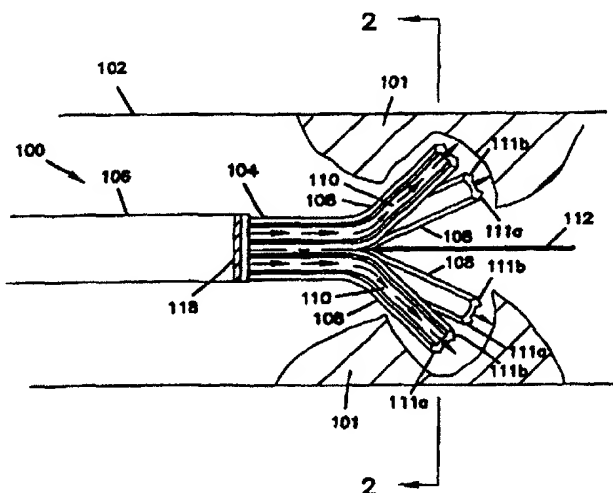


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(54) Title: CATHETERS FOR GUIDING DRUGS BY DEPLOYABLE GROOVES



(57) Abstract

Catheters for delivering drugs or other agents within a lumen, such as an artery or vein, are disclosed. In one embodiment, a catheter comprises an outer shaft (106) with a lumen extending longitudinally therethrough. An inner shaft (104) is slidably received within the outer shaft (106). A distal portion of the inner shaft comprises a plurality of grooved delivery members (108) having a non-deployed position wherein the delivery members (108) lie within and are compressed by the outer shaft, and a deployed position wherein the delivery members extend beyond the outer shaft. In the deployed position wherein the delivery members flare outward at an angle, beyond the diameter of the outer shaft to bear against a site of interest, i.e., a thrombus (101) or a vessel wall. Drugs or other agents can be conveyed to the delivery members (108) through a space between the inner and outer shafts.

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CATHETERS FOR GUIDING DRUGS BY DEPLOYABLE GROOVES

Field of the Invention

5 Drug delivery catheters and, more particularly, drug delivery catheters with self-expanding drug delivery portions comprising grooves which guide drugs or other agents towards an intended site, are disclosed. Examples of possible sites include the walls of lumens or vessels such as arteries or veins, or obstructions in such lumens or vessels, such as a thrombus.

Background of the Invention

10 It is often necessary to deliver drugs to a particular site within a body. For example, catheters are used to deliver drugs or other agents to lumens or vessels within the cardiovascular system, the urethra, bladder, prostate, rectum and central nervous system, such as the spinal cord.

15 Thrombosis, the formation of a clot or thrombus in the cardiovascular system from the constituents of blood, is a potentially life threatening condition. Thrombosis can develop in any part of the cardiovascular system, but is most common in veins, particularly the deep veins in the leg. Thrombosis can result from a variety of causes including poor circulation, trauma, prolonged bed rest, or hip surgery, for example. In the arteries, thrombosis can be caused by arteriosclerosis. 20 Thrombosis can develop in cerebral vessels, as well.

 If a portion of the thrombus separates and is transported through the cardiovascular system, it can cause an embolism, or blockage of a blood vessel. A thrombus in a deep vein in the leg can cause a pulmonary embolism. A thrombus in 25 a coronary artery can cause myocardial infarction. Similarly, a thrombus in a cerebral artery can cause cerebral infarction.

 During the early development of thrombosis, up to about seven days, the thrombus is soft and can be treated by a variety of techniques. Drug delivery catheters have been used to provide thrombolytic drugs or agents such as urokinase, 30 streptokinase and recombinant tissue type plasminogen activator (rTPA), directly onto and into a thrombus. The FasTracker infusion catheter from Target Therapeutics®, for example, comprises a catheter shaft with a drug delivery lumen extending through the shaft. A drug delivery port is located at the distal end of the

shaft. To dissolve a thrombus, the FasTracker can be advanced through the thrombus and then withdrawn back through the thrombus as a thrombolytic drug or agent is delivered into the thrombus. This process can be repeated several times. Such a catheter has several disadvantages. For example, it can be difficult to center
5 within the thrombus. In addition, as the thrombus dissolves, the catheter could be drawn to one portion of the vessel by gravity, preventing even delivery of drug to other portions of the thrombus. A catheter which could apply thrombolytic agents evenly to all portions of a thrombus would be advantageous.

In alternative treatments, a pulse spray of a lytic agent, such as
10 urokinase, has been directed onto soft thrombi to mechanically break up and dissolve them. High pressure water has also been directed onto the thrombus to destroy it. The thrombus can also be broken by a laser or a drill. The broken or dislodged portions of the thrombus may be aspirated through a catheter so that they cannot migrate and obstruct other vessels of the cardiovascular system. Results have
15 been mixed, with some treatments damaging tissue, causing another thrombotic or stenotic process. A surgical procedure may be required to remove the thrombus, as well.

It has been found that the application of lytic agents to a clot under pressure provides improved results over diffusion. Blinc, A., et al., "Dependence of
20 Blood Clot Lysis on the Mode of Transport of Urokinase into the Clot - - A Magnetic Resonance Imaging Study In Vitro," Thrombosis and Haemostasis, 65(5) 549-552 (1991). International Patent Application No. PCT/US96/15449, assigned to the Applicant of the present invention, discloses driving a drug or other agent through the thrombus by pressure, withdrawing and filtering the thrombic material
25 and delivered drug, and recycling the drug.

In other cardiovascular applications, various types of agents are being investigated for use in preventing restenosis of an artery after percutaneous transluminal coronary angioplasty (PTCA) or percutaneous transluminal angioplasty (PTA). Heparin, an anticoagulant and inhibitor of arterial smooth muscle
30 proliferation, is one such drug. Dexamethasone may also prevent smooth muscle proliferation. Other drugs and agents are being investigated for efficacy, as well. Such drugs can be delivered before or after the angioplasty procedure. The delivery

of lytic agents such as urokinase, streptokinase and recombinant tissue type plasminogen activator (rTPA) to dissolve plaque in arteries and veins is also being investigated.

Because of blood flow through the artery, drugs delivered to the site of an angioplasty procedure, for example, can be rapidly dissipated and removed from the delivery site before they can be absorbed in sufficient quantities to become effective. Catheters have therefore been developed to directly deliver drugs to the desired site and maintain them there. For example, U.S. Patent No. 5,087,244 to Wolinsky et al., discloses a catheter with a flexible balloon having a plurality of minute openings. The balloon can be inflated by heparin. As the walls of the balloon contacts the arterial wall, the heparin exits the balloon, directly on the walls. The balloon can block the perfusion of blood distal to the delivery site, depriving tissue of needed blood. This limits the amount of time available for drug delivery. The inflation of the balloon can also damage the arterial wall, promoting restenosis. In addition, since the balloon is inflated by the heparin, heparin can leak out before the arterial wall is contacted, wasting the drug. The balloon also needs to be deflated prior to removal or to allow blood flow. The pressure required to deflate the balloon could draw blood into the balloon, preventing further use of the catheter until the blood has been removed.

U.S. Patent No. 4,824,436, also to Wolinsky, discloses a drug delivery catheter comprising a pair of occlusion balloons for securing the catheter in position and isolating a region of the artery which has been opened by PTCA, and a drug delivery conduit for delivering heparin under pressure into the region isolated by the occlusion balloons. The pressure of the heparin forces the heparin to coat and penetrate the arterial tissue. This configuration presents the similar perfusion problems to those discussed above. The heparin, therefore, is only delivered for 5-60 seconds, which may be inadequate for sufficient absorption.

U.S. Patent No. 5,336,170 to Kaplan et al., discloses a catheter with drug delivery ribs which are brought into contact with the walls of the body lumen by an inflatable balloon. A series of ports in the catheter shaft can be provided proximal to the balloon to allow for perfusion of blood through the catheter shaft. As above, inflation of the balloon can damage the wall of the lumen.

One commercially available drug delivery product is the DISPATCH™ from Scimed. The DISPATCH™ includes an inflatable polyurethane coil which provides a path for blood to flow and defines regions proximate the wall of the vessel into which drug is delivered. While apparently allowing for significant perfusion, the device is complex and therefore difficult to use and manufacture. The inflatable coil can also prevent portions of the artery from being exposed to the drug and block perfusion to side branch arteries.

It is known that the velocity of fluid flow through a tube varies across the axial cross-section of the tube. The velocity is maximum at the center of the tube and approaches zero at the walls. In an artery or a vein, blood flow is very slow in the region proximate the walls. If drugs or other agents could be effectively delivered proximate the walls, the blood flow can atraumatically carry the delivered drug or agent over the site of interest. The delivered drug or agent would also not dissipate as rapidly as drug delivered to the center of the vessel. Less drug could then need to be delivered, shortening procedures and decreasing their cost.

United States Serial No. 08/483,201, filed on June 7, 1995, and International Patent Application No. PCT/US96/08861, and assigned to the Applicant of the present invention, disclose drug delivery catheters with self-expanding drug delivery portions comprising a plurality of resilient members. A shaft, sleeve or other restraining means compresses the drug delivery portion until the drug delivery portion is proximate the site of interest. The restraining means is then retracted or removed, allowing the drug delivery portion to expand radially to bear against the wall of the vessel. Drugs or other agents can then be delivered through lumens in each member.

Drugs and other agents are delivered to lumens, vessels and cavities in other portions of the body, such as the urethra, bladder, prostate, rectum, bile duct, pancreatic duct and central nervous system, such as along the spinal column, to treat a variety of conditions, as well.

Summary of the Invention

A catheter is disclosed comprising self-expandable delivery members with grooves which are compressed while the catheter is advanced to a site within a lumen, such as an artery or a vein, for example. When deployed at a desired site, the

delivery members are released to bear against the site, which can be an obstruction in a lumen, such as a thrombus, or the walls of the lumen itself.

In accordance with one embodiment of the invention, a catheter for delivering drugs or other agents within a lumen is disclosed comprising an outer shaft having a lumen extending longitudinally therethrough and an inner shaft slidably received within the lumen of the outer shaft. The inner shaft has a distal portion and a proximal portion. The distal portion comprises a plurality of grooved resilient delivery members. The delivery members have a non-deployed position compressed by the outer shaft when the delivery members are within the outer shaft and a deployed position when the delivery members extend out of the outer shaft, wherein in the deployed position the delivery members flare outward beyond the outer shaft at an angle. The inner and outer shafts define a space between them through which the drug or agent is conveyed to the grooves of the delivery members.

In accordance with another embodiment of the invention, a catheter is disclosed comprising an outer shaft having a lumen extending longitudinally therethrough and an inner shaft slidably received within the lumen of the outer shaft. A plurality of grooved delivery members are provided having distal portions coupled to the inner shaft at a first location and proximal portions coupled to the outer shaft at a second location. The first location is proximal to the second location. The delivery members have a length such that the delivery member has a non-deployed position when the first and second locations are separated by a distance approximately equal to the length of the delivery member, and a deployed position when the first and second locations are separated by a distance less than the length of the delivery member. The delivery members have central portions between the proximal and distal portions which extend outward beyond the outer shaft in the deployed position.

A catheter for delivering drugs or other agents to a site within a lumen is also disclosed comprising a delivery portion having a first shaft with a distal portion and at least one resilient grooved delivery member at the distal portion. The delivery member has a deployed position wherein the delivery member bears against the site and a non-deployed position wherein the delivery member does not bear against the site. Means are provided for deploying the delivery member from

the non-deployed position to the deployed position. Means are also provided for conveying a drug or agent through the catheter, to the delivery member.

Description of the Figures

Fig. 1 is a side view of a catheter in accordance with one embodiment
5 of the present invention, deployed within a thrombus in an artery;

Fig. 2 is a front view of the catheter through line 2-2 of Fig. 1;

Fig. 3 is a partial cross-sectional view of the catheter of Fig. 1, in a
non-deployed position;

Fig. 4 is a cross-sectional view of a manifold for use with the catheter
10 of Fig. 1;

Fig. 5 is a front view of a shaft from which grooved delivery
members of the catheter of Fig. 1 can be formed;

Fig. 6 illustrates several steps in the formation of the delivery
members of Fig. 1;

Fig. 7 is a side view of a second embodiment of the present invention
15 in a deployed position;

Fig. 8 is a cross-sectional view of the catheter of Fig. 7, through line
8-8;

Fig. 9 is a side view of the catheter of Fig. 7, in a non-deployed
20 position;

Fig. 10 is a side view of a catheter in accordance with one
embodiment of the present invention, wherein a thread compresses the delivery
members;

Fig. 11 is a side view of the catheter in accordance with one
25 embodiment of the present invention, wherein the thread extends through a guide
wire unit;

Fig. 12 is a cross-sectional view of the catheter in accordance with
one embodiment of the present invention, wherein the thread extends through a
groove in a delivery member;

Figs. 13A-13E illustrate the formation of a releasable knot for use
30 with the embodiments of Figs. 10-12;

Fig. 14 is a side view of a tool used in the manufacture of the catheter of Fig. 7; and

Fig. 15 is a cross-sectional view of the tool of Fig. 14, in position during the manufacture of the catheter of Fig. 7.

5

Description of the Invention

Fig. 1 is a side view of a catheter 100 in accordance with one embodiment of the present invention, deployed to deliver drugs or other agents to a thrombus 101 within a cerebral artery 102, for example. The thrombus 101 is shown partially dissolved, as described below. The catheter comprises an inner shaft 104
10 slidably received within an outer shaft 106. The inner shaft 104 has a distal portion comprising one or more resilient delivery members 108 which when deployed flare outward from the inner shaft 104 at an angle, beyond the diameter of the outer shaft 106 and towards the walls of the artery 102. Each delivery member 108 comprises a longitudinal groove 110. The groove 110 may be defined by walls 111a, 111b. Four
15 delivery members 108 are provided in this embodiment. The catheter 100 is preferably advanced to the site of interest over a guide wire 112. The guide wire 112 is preferably received within a lumen 114 extending longitudinally through the inner shaft 104. A front view of the lumen 114 is shown in Fig. 2.

Fig. 2 is a front view of the deployed catheter 100 and the artery 102
20 along line 2-2 of Fig. 1, through the thrombus 101. The walls 111a, 111b of the deployed delivery members 108 are shown bearing against the wall of the thrombus 101. The distal edge of the outer shaft 106 is also shown.

Fig. 3 is a partially cutaway side view of the catheter 100 of Fig. 1, in a non-deployed position within the artery 102. The delivery members 108 lie
25 completely within the outer shaft 106, a portion of which is shown in cross-section. In this embodiment, the outer shaft 106 compresses the delivery members 108, maintaining them within the inner diameter of the outer shaft 106 while the catheter 100 is stored, advanced to a desired site and, optionally, when the catheter 100 is withdrawn. When the distal end of the catheter 100 is properly positioned at the site
30 of interest, as discussed below, the delivery members 108 can be released by retracting the outer shaft 106, allowing the delivery members 108 of the distal

portion to flare outward beyond the outer diameter of the outer shaft 106.

Alternatively, the inner shaft can be advanced to release the delivery members 108.

The outer wall of the inner shaft 104 and the inner wall of the outer shaft 106 preferably define a space 116 extending from the proximal end of the catheter 100 through the catheter 100 to the delivery members 108 through which drugs are conveyed through the catheter 100 to the grooves 110.

The inner shaft 104 preferably includes a smooth portion 104a proximal to the delivery members 108. A smooth shaft causes less friction with the delivered drug or agent, which can slow fluid flow. In a catheter of about 145 cm, for example, the grooves 110 preferably extend about 20 cm from the distal tip of the inner shaft 104. The remainder of the inner shaft 104 is preferably smooth. After traversing the length of the outer shaft 106, the drugs are channeled into the grooves 110 of the delivery members 108. The drugs then follow the grooves to the site of interest, as shown by the arrows in Fig. 1.

If desired, however, the grooves 110 can extend the entire length of the inner shaft 104. In that case, a larger space 116 may be required to achieve an adequate flow rate. While the term "drug" is generally used hereafter, it is understood that other agents can be delivered as well.

The catheter 100 in accordance with the present invention can have an outer diameter of approximately 0.038 inches, for example. This is small enough to be advanced through and to treat conditions in cerebral arteries, which typically have diameters ranging from about 1.0-4.5 mm. The inner diameter of the outer shaft 106 is preferably about 0.031 inches. The outer diameter of the smooth portion of the inner shaft is preferably about 0.026 inches, defining the space 116 with a height of about 0.005 inches. The inner diameter of the inner shaft 104 is preferably about 0.017 inches. The outer diameters of the walls 111a, 111b of the grooves 110 are preferably about 0.029 inches. The outer diameters of the grooves 110 themselves are preferably about 0.023 inches. The height of each wall 111a, 111b from the inner diameter is preferably about 0.006 inches. The width of each groove 108 is preferably about 0.009 inches. The length of the grooved distal portion of the inner shaft 104 is preferably about 20 cm. The length of the expandable delivery members 108 is about 5.0 mm. The dimensions of the catheter 100 may also vary

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dependent upon the diameter of the intended site. For example, a larger diameter catheter with longer delivery members 108 may be desired for a site with a larger diameter.

Drugs can be delivered through lumens in the inner or outer shaft as well. Such shafts could be formed in a multi-lumen extrusion process. Such multi-lumen shafts could, however, increase the outer diameter of the catheter 100, making it inappropriate for certain applications, such as within the smaller cerebral arteries.

The number of delivery members 108 can vary. The preferred number can depend on the diameter of the vessel where the drug is to be delivered. For example, four delivery members 108 are preferably provided in this embodiment, which will enable an even distribution of the delivered drug to the thrombus 101 in a cerebral artery 102. Additional delivery members 108 could be preferred for larger vessels, such as the coronary arteries or deep veins in the leg.

The angle of the flare of the delivery members 108 with respect to a longitudinal axis of the inner shaft 104 when fully deployed outside of a lumen is preferably about 90°. The preferred angle of 90° ensures that the delivery members 108 will rotate through the entire cross-section of the vessel or lumen, even if the catheter 100 is not centered within the thrombus or even if the delivery members 108 are deployed within a curved portion of the vessel or lumen. The delivery members 108 preferably have a length such that when fully expanded within the vessel, the distal portions of the delivery members bear against the vessel walls.

The outer shaft 106 preferably includes a radiopaque band 118 of gold, tantalum, platinum or iridium, for example, proximate its distal end, to assist in tracking the progress of the catheter on a fluoroscope during a procedure, as is known in the art. The inner shaft 104 may also include a radiopaque band 119 to assist in determining whether the outer shaft 106 has been sufficiently retracted. Preferably, the marker band 119 is positioned about 15 mm from the distal end of the delivery members 108. When the band 118 is approximately aligned with the band 119, the outer shaft 106 has been sufficiently retracted.

The distal portion of the inner shaft 104, particularly the delivery members 108, is preferably a soft, flexible, resilient material which can be advanced through the turns of the vascular system and be deployed without damaging the

vessel walls. The material must also be capable of being heat set in an expanded position and compressed by the outer shaft when not deployed. Despite its softness, however, it must have sufficient pushability and torqueability to respond to the control of the surgeon. Low density polyethylene (LDPE), such as LDPE 640 resin from The Dow Chemical Company, is preferred. Typical property values for LDPE 640 appear below:

RESIN PROPERTIES		TEST ASTM METHOD	VALUES
10	Melt Index g/10 min.	D 1238	2.0
	Density, g/cc	D 792	0.922
	Tensile Yield, psi (MPa)	D 638	1600(11)
	Ultimate Tensile, psi (MPa)	D 638	1600(11)
15	Ultimate Elongation, %	D 638	600
<u>BLOWN FILM PROPERTIES @ 1.5 MIL</u>			
20	Dart Impact, g	D 1709	100
	Elmendorf Tear, g	MD D 1922	400
		CD	275
	Tensile Yield, psi (MPa)	MD D 882	1600(11)
		CD	1550(10.7)
25	Ultimate Tensile, psi (MPa)	MD D 882	3300(22.7)
		CD	2700(18.6)
	Ultimate Elongation, %	MD D 882	325
		CD	575
	Gloss, 45°	D 2457 65	
30	Haze, %	D 1003	6
	Coefficient of Friction	D 1894	0.8

The smooth, proximal portion of the inner shaft 104 is preferably a stiffer material than the delivery portion, for improved pushability and torqueability. The smooth portion can be high density polyethylene (HDPE), for example. A suitable HDPE is Petrothene® LM 6007-00 from Quantum Chemical Co., Cincinnati, Ohio. The two portions of the inner shaft 104 can be connected by adhesive or thermal bonding, as is known in the art. Typical property values for Petrothene® LM6707-00 appear below:

	<u>PROPERTY</u>	<u>ASTM TEST METHOD</u>	<u>VALUE</u>
	Density, g/cm ³	D 1505	0.960+
5	Melt Index, g/10 min.	D 1238	0.7
	Tensile Strength @ Break, psi	D 638	4,400
	Elongation @ Break, %	D 638	>600
	Flexural Modulus, psi	D 790	220,000
	Tensile Impact, ft-lb/in.	D 1822	100
10	Low Temperature Brittleness, F ₅₀ °C	D 746	<-76
	Heat Deflection Temperature, @ 66 psi, °C	D 648	78
	Vicat Softening Point, °C	D 1525	125
15	Hardness, Shore D, °C	D 2240	68

For adequate flexibility and to protect vessel walls, the distal portion of the outer shaft 106 is also preferably a softer material than the proximal portion. The material of the distal portion of the outer shaft 106 should also have an elongation appropriate to prevent excessive stretching of the outer shaft 106 when the outer shaft is moved with respect to the inner shaft 104. Excessive stretching could impede release of the delivery members 108.

A blend of about 60% LDPE, 30% HDPE and 10% ethyl vinyl acetate (EVA) is preferred for the distal portion of the outer shaft. The LDPE and EVA are softer materials. Sufficient tracking is provided by the HDPE. ELVAX 750 from DuPont Co., for example, is an appropriate EVA. The LDPE and HDPE described above may be used, as well. Typical property values for ELVAX 750 appear below:

30	Melt Index dg/min ASTM - D1238		7.0
	Vinyl Acetate, wt.% TGA		9.0
35	Density, kg/m ³ (g/cm ³) ASTM - D792		930(0.930)
40	Tensile Strength MPa (psi) ASTM - D638 (Test Specimen = ASTM D638, type IV; crosshead speed = 5.1 cm (2 in/min))	-20°C 23°C 49°C	21(3,100) 15(2,200) 9.6(1,400)

Elongation, %			
5	ASTM D638		
	(Test Specimen =	-20°C	450
	ASTM D638, type IV;	23°C	600
	crosshead speed =	49°C	550
5.1 cm (2 in/min))			
Vicat Softening Temp.			
10	ASTM - D1525		73(167)
Flexural Modulus MPa (psi)			
ASTM D790			
15		-20°C	363(52,500)
		23°C	86(12,500)
		49°C	6(6,700)
Stiffness MPa (psi)			
ASTM - D747			
20		-20°C	205(29,700)
		23°C	74(10,800)
Hardness Shore			
ASTM - D2240			
25		Scale A	95
		Scale D	47
Brittleness Temp.			
ASTM - D746			
30		°C	<-100
		°F	<-148
Compression Set, %			
ASTM - D395,			
35	Method B	10 days at 25°C	46
		22 hrs. at 70°C	74
Tensile Impact,			
kJ/m ² (ft-lb/-in ²)			
40	ASTM - D1822		
		-20°C	305(145)
		23°C	400(190)

45 The distal portion of softer material of the outer shaft 106 preferably has a length of about 18 cm, for example. The two portions of the outer shaft can be connected by adhesive or thermal bonding, as is known in the art.

The materials preferred for the inner shaft 104 and the outer shaft 106 also slide easily with respect to each other. To further ease the movement of one shaft with respect to the other, a lubricious coating of silicone (not shown) for example, is preferably provided between the inner shaft 104 and outer shaft 106.

5 Other non-thrombogenic materials which can be used for the inner and outer shaft include thermoplastic elastomer resins such as polyether block amide (PEBA), polytetrafluoroethylene (PTFE), polyester elastomers, polyethylene, fluorinated ethylene propylene (FEP), polyimide and all the known grades of polyethylene such as linear low density polyethylene, LDPE, HDPE and
10 ultra high density polyethylene. The proximal portions of the inner shaft 104 and outer shaft 106 could be steel or nitinol, as well, as long as it is flexible enough.

If the preferred materials for the outer shaft 106 and the inner shaft 104 are not rigid enough to be easily advanced along the guide wire 112 through a guide catheter, a reinforcing sleeve of stainless steel, titanium, or titanium nickel,
15 for example, may be provided within the guide wire lumen 114. Such a reinforcing sleeve may extend from the proximal end of the catheter 100, more than half the length of the catheter up to about 12 inches or about 30 mm from the distal end of the inner shaft 104.

Other means of reinforcing the catheter can be used as well, as is
20 known in the art. For example, the outer shaft 106 can be reinforced instead of the shaft 104. A rigid wire or stylet can also be embedded within either shaft 106, 104. Irradiation of the shafts with an electron beam to increase the cross-linking and hence the stiffness of the polymeric material, can also be used. A harder material can also be used for the outer shaft 106 or inner 104 than those preferred above, in
25 which case the distal portion of the sleeve or shaft may need to be "necked down" to decrease its outer diameter, increasing its flexibility. This technique could be used instead of providing different materials for the distal and proximal portions of the outer shaft 106.

Fig. 4 is a cross-sectional view of the proximal portion of the
30 catheter 100, including a manifold 124 for introducing a drug or other agent into the space 116 between the outer and inner shafts 106, 104. The drug is supplied from a drug infusion unit or a syringe (not shown) through a first port 128

depending from a sleeve 129. The guide wire 112 can extend through a second port 130. A collar 132 at the proximal end of the catheter 100 is attached to the outer shaft 106 to advance or retract the outer shaft. The outer shaft 106 is adhesively bonded, for example, to the collar 132.

5 A seal, such as an O-ring 138 of latex or silicone, for example, is preferably provided between the manifold and proximal portion of the outer shaft 106 to prevent leakage. A seal cap 140 secures the seal 138 in place. The seal cap 140 can also act as a stop engaging the collar 132 to prevent excessive retraction of the outer shaft 106. The outer shaft 106 is retracted by holding the sleeve 129
10 stationary and withdrawing the collar 132 a sufficient distance so that the distal portion of the outer shaft 106 is no longer compressing or restraining the delivery members 108. As discussed above, this can be observed on a fluoroscope by the alignment of the bands 118, 119. As it is being retracted, the proximal portion of the outer shaft 106 moves within the chamber 129a of the sleeve 129, bearing
15 against the seal 138. Advancing the collar 132 advances the outer shaft 106 back over the delivery members 108. Alternatively, the sleeve 129 could be retracted with respect to the collar 132, to withdraw the inner shaft 104. A shoulder 136 is preferably provided to limit the forward advance of the outer shaft 106.

 Effective drug delivery generally requires at least 10cc/hour at up to
20 45 psi. The drug delivery catheter in accordance with the present invention can deliver about 30cc/hour at 10 psi. Drugs or agents can be delivered through the guidewire port 130 and guidewire lumen 114, as well.

 In use, the catheter 100 of the invention can be advanced to the site of interest over the guidewire 112 through a guide catheter (not shown). The
25 location of the distal end of the catheter 100 can be followed on a fluoroscope via the band 118, as is known in the art. When the catheter 100 is properly positioned within the thrombus 101, the outer shaft 106 can be retracted by withdrawing the collar 132 a sufficient distance to align the band 118 with the band 119. Initially, the delivery members 108 will remain essentially compressed by the thrombus 101.
30 The drug or other agent is then delivered through the port 128 of the manifold 124, into the space 116 and through the catheter 100, into the grooves 110. From the grooves 110, the drug is delivered onto the surrounding thrombus 101. The

delivered drugs will dissolve the portion of the thrombus 101 surrounding the delivery members 108. As the thrombus dissolves, each of the delivery members 108 will gradually flare further outward, continuing to bear against the thrombus 101 as additional drug is delivered. The thrombus 101 will thereby be dissolved
5 evenly, from approximately the center of the thrombus 101 towards its periphery adjacent the walls of the vessel 102. Blood flow through the dissolved portion of the thrombus 101, between the delivery members 108, can resume quickly.

Depending on the length of the thrombus 101 and the length of the delivery members 108, it may be desirable or necessary to slowly withdraw the
10 delivery members 108 through the thrombus by retracting the catheter 100 while the drug is being delivered. It may also be necessary or desirable to completely remove the delivery members 108 from the thrombus 101, compress them by the outer shaft 106, reposition the delivery members 108 within the thrombus, retract the outer shaft 106 again and resume drug delivery.

15 As mentioned above, additional drug delivery can be provided through the guidewire lumen 114. It may be necessary to withdraw the guidewire 112 to obtain adequate flow. Drugs or other agents delivered through the guidewire lumen 114 have been observed to follow the underside of the groove 110. It is believed that the delivery of drugs over the delivery members 108,
20 through the grooves 110, creates a region of low pressure on the underside of the delivery members 108, which draws the delivered drug through the guidewire lumen 114.

When the thrombus is sufficiently dissolved, the outer shaft 106 can be advanced back over the distal portion of the inner shaft 104 or the inner shaft
25 104 can be withdrawn into the outer shaft 106. The catheter 100 can then be removed through the guide catheter. It is also possible to remove the catheter 100 through the guide catheter while it is in the deployed position.

The catheter 100 of the present invention can also be used to deliver drugs or agents to the walls of a lumen or vessel, such as to the slow flow portion
30 of an artery. Anticoagulants and antiproliferative agents, for example, can be advantageously delivered to the site of a PTCA or PTA procedure to prevent restenosis, for example. A thrombus may be dissolved by delivering thrombolytic

agents to the slow flow portion of the vessel, as well. Drug delivery through the guidewire lumen 114, could contribute to dissolution of the thrombus in conjunction with delivery to the vessel walls.

For delivery to the wall of a vessel or lumen, the delivery members 108 preferably have a length such that when released, the delivery members will bear against the wall of the lumen or vessel at an angle. Preferably, the drug is delivered upstream of the site with respect to the blood flow so that the slow blood flow proximate the wall atraumatically carries the drug over the site. The delivered drug can travel through the distal end of the groove 110 onto the vessel wall, or over the walls 111a, 111b, themselves.

When deployed, the delivery members 108 are separated by sufficient space to allow for significant perfusion of blood between the members. This increases the possible length of surgical procedures, without requiring perfusion means which can increase the complexity of the use and manufacture of the catheter.

In addition, other devices, such as aneurysm coils or dilatation catheters, can be delivered through the catheter 100. Either the instrument can be delivered through the lumen of the inner shaft 104, or the inner shaft 104 can be completely removed from within the outer shaft 106 to enable the delivery of other such devices through the lumen of the outer shaft 106. The manifold can be easily modified to enable the insertion of such devices, as is known in the art.

To manufacture the catheter 100 of the first embodiment of the present invention, a grooved shaft 200 comprising the desired material or composition for the delivery members 108 is extruded with a length of approximately 20 cm. Fig. 5 is a front view of the shaft 200. The grooves 110 and walls 111 can be formed in the shaft through a conventional extrusion process.

The delivery members 108 are formed by cutting through the walls 111 of the extruded shaft approximately along the dotted lines 202 the desired length of the delivery members 108, here about 5.0 mm. A blade or other thin cutting device is preferred. The shaft can be cut radially or longitudinally by hand or by a machine. Radial cutting from the outside of the shaft through to the inner lumen of the shaft, is preferred. The machine can include a mounting for securing

the shaft and a series of cutting blades disposed radially to simultaneously cut the distal portion of the shaft along its longitudinal axis. The number of blades corresponds to the number of delivery members desired. The thickness of the blades is preferably less than 0.010 inches. A thickness of about 0.005 inches or less is most preferred. The shaft is preferably supported on a mandrel while being cut. The shaft can be cut with a laser, as well.

As mentioned above, the length of the delivery members 108 can vary depending on the application. The length of all the delivery members is preferably the same, which enhances the ability of the members to deploy after retraction of the sleeve.

To form the flare of the delivery members 108 in the first embodiment, a tool, such as the tool 300 shown in Fig. 6, is inserted within the guidewire lumen 114 of the extruded shaft 200, after the walls 111 are cut, as shown in Fig. 6. The tool 300 preferably comprises a rod shaped guiding mandrel or wire 302 depending essentially perpendicularly from a flat surface 304. A curved portion 306 is preferably provided between the mandrel or wire and the flat surface 304. The shaft 200 is advanced over the mandrel 302 in the direction of arrow A. As the distal ends of the delivery members 108 engage the curved surface 306, they are forced outward, along the flat surface 304, as indicated by the dotted lines 308 in Fig. 6. The tool 300 is advanced to the uncut portion of the shaft. When the tool 300 is suitably positioned with respect to the delivery members 108, a second tool 310 is preferably placed over the mandrel 302, the shaft 200 and delivery members 108 to secure the delivery members 108 against the flat surface 304. The assembly is heated in an oven or on a hot plate to about 65-70°C for about 30-60 seconds, to heat set the delivery members 108. In this embodiment, the angle of the flare is preferably about 90°. If a maximum flare of less than 90° is desired, the tool 300 can have a conical surface instead of a flat surface 304. The second tool 310 would have a matching surface. The tools 300 can be made of brass, stainless steel or PTFE, for example.

After heat setting, the shaft comprising the delivery members is coupled to the smooth portion of the inner shaft 104 by an adhesive or thermal

bonding, as is known in the art. The inner shaft can be extruded in a conventional manner.

While an outer shaft is preferred, other methods for compressing or restraining the delivery members may be provided. For example, a thread can be used to tie the delivery members together with a releasable knot. The thread can extend through a lumen of a shaft such as the guidewire lumen. The shaft would also then preferably comprise drug delivery lumens extending longitudinally through the shaft. The lumen openings at the distal end of the shaft could be aligned with the grooves of the delivery members 108, which would be attached to the distal end of the inner shaft. The use of a releasable knot to restrain expandable drug delivery members is disclosed in Figs. 10-13. The releasable knot is also disclosed in PCT/US96/08861 and U.S.S.N. 08/483,201, incorporated by reference herein.

Figs. 10-13 show this variation in the embodiment of Figs. 1-3, wherein instead of the outer shaft 106, a thread 141 restrains and compresses the delivery members 108. The thread 141 can be tied around the periphery of the delivery members 108, in a releasable knot 142, such as a horse thief's knot, shown in Fig. 13E. Formation of a horse thief's knot is shown in Figs. 13A-13D. First, a loop 144 is formed at one end of the thread 141, beneath the delivery members 108. For illustrative purposes, the delivery members are not shown in these views. The loop 144 has a short end 146 and a long end 148. A portion 150 of the short end 146 is carried over the members and beneath the loop 144 as shown in Fig. 13B, to form a second loop 152, as shown in Fig. 13C. The long end 148 is then carried under the short end 146, over the first loop 144 and through the second loop 152. The short end 146 is pulled to tighten the knot. Pulling the long end 148 releases the knot, allowing the delivery members 108 to flare to their deployed position.

The long end 148 of the thread 141 can extend over the exterior of the shaft 104 as shown in Fig. 10, through a lumen within the shaft 104, such as the guide wire lumen 114, as shown in Fig. 11 or through a groove 110 as shown in Fig. 12. The guide wire lumen 114 can be divided into two lumens, one for the guide wire 112 and one for the thread 141. The thread 141 can be nylon, for

example. The thread can have a diameter between about 0.005-0.008 inches, for example. The use of a thread 141 to compress the delivery members instead of the outer shaft decreases the outer diameter of the distal portion of the catheter and may therefore be particularly suited for use in small vessels, such as cerebral
 5 arteries which can be diameters of about 1.0-2.5 mm, for example. The proximal portion of the catheter as shown in Fig. 4 can be suitably modified for use with this embodiment. For example, no collar 132 is required to retract the outer shaft 106.

Multi-lumen shafts with drug delivery lumens could also be used in the present invention. Such multi-lumen shafts could be used with an outer shaft
 10 or sleeve to restrain the delivery members and enable drug delivery through the shaft, as well. The shaft can be extruded in a multi-lumen extrusion process, as is known in the art. One or both ends of the extrusion can have a tapered portion leading to a wider longitudinal region, to ease subsequent operations on the shaft. Such wider regions can be formed by a bump extrusion process, also known in the
 15 art.

Fig. 7 is a side view of a catheter 400 in accordance with a second embodiment of the present invention which does not require a retractable sheath. Here, distal portions 402 of each of the delivery members 404 are coupled to an inner shaft 406 and proximal portions 408 (shown in Fig. 8 and in phantom in Fig.
 20 7), are coupled to an outer shaft 410. The inner shaft 406 is slidably received within the lumen of outer shaft 410. The inner shaft 406 preferably includes a lumen 416 (shown in Fig. 8) for receiving a guidewire 412.

The outer surface of the walls 417 of the grooves 418 of the proximal portions 408 of the delivery members 404 can be coupled to the inner
 25 surface 414 of the outer shaft, as shown in the cross-sectional view of Fig. 8. Fig. 8 shows the guidewire lumen 416 of the inner shaft 406, as well. As above, the coupling can be thermal or adhesive. The grooves 418 will extend into the space between the inner and outer shafts. Drugs delivered through the space will enter the grooves and be conveyed to the desired site, as indicated by the arrows in Fig.
 30 7. The proximal portions 408 of the delivery members 404 preferably fit snugly over the inner shaft 406 to prevent leakage. The distal and proximal portions of the delivery members 404 are preferably integral.

When not deployed, the locations of the couplings are separated by a distance L approximately equal to the length of the delivery members 404 themselves, as shown in Fig. 9. To deploy the delivery members, the inner shaft 406 is retracted or the outer shaft 410 is advanced, decreasing the distance between the couplings. As the distance between the distal and proximal portions decrease, central portions 420 of delivery members 404 buckle outward beyond the outer diameter of the outer shaft 410. When the inner shaft is fully extended again, the delivery members also become fully extended, lying adjacent to the inner shaft.

This embodiment provides positive mechanical control over the deployment and retraction of the delivery members. It also enables dilatation of the vessel wall.

The catheter 400 of this embodiment can be manufactured of the same materials as the first embodiment. To manufacture the second embodiment of the present invention, a grooved shaft with a lumen is extruded. A wire is then inserted through the lumen. A series of longitudinal cuts which do not extend to the proximal or distal ends of the shaft are then made with a cutting blade or razor through the shaft, to the lumen, to define the delivery members 404. Heat setting is not necessary. If heat setting is desired, however, an oblong shaped tool made of brass, stainless steel or PTFE, for example, can be inserted between the delivery members. A perspective view of such a tool 714 is shown in Fig. 14. A cross-sectional view of the tool 714 is shown in Fig. 15 of those applications. The tool preferably includes an opening 716 along its longitudinal axis for receiving a wire 718 inserted through the distal end of the shaft. The wire 718 helps to maintain the tool 714 centered between the delivery members 706. The shaft and tool 714 can then be heated in an oven.

Examples of drugs or agents which can be delivered through the catheters and methods of the present invention include substances which inhibit platelet deposition and thrombus formation or promote thrombolysis and thrombus dissolution, such as plasmin, tissue plasminogen activator (tPA), single chain prourokinase (scuPA), prostaglandins, cyclooxygenase inhibitors, phosphodiesterase inhibitors, thromboxane synthetase inhibitors; antagonists of

glycoprotein receptors including (GP) Ib, GP IIb/IIIa, antagonists of collagen receptors, and antagonists of platelet thrombin receptors, for example.

Alternatively, the drugs or agents delivered by the systems and methods of the present invention can directly affect platelet metabolic function.

- 5 Examples of such substances include prostaglandins, cyclooxygenase inhibitors, phosphodiesterase or thromboxane synthetase inhibitors, inhibitors of calcium transport, or elevators of cyclic adenosine monophosphate (cyclic AMP).

- Examples of anticoagulants which can be delivered by the catheters and methods of the present invention include heparin, hirudin, hirulog, hirugen,
10 activated and non-activated protein C, synthetic or naturally occurring antagonists of thrombin, and Factor Xa, or other activated or non-activated coagulation protease inhibitors and coagulation factors, e.g., FIX, FVIII, FV, FVIIa and tissue factor.

- Examples of antiproliferatives which can be delivered by the
15 catheters and methods of the present invention include dexamethasone, growth factor, a growth factor inhibitor, growth factor receptor antagonist, transcriptional repressor, translational repressor, antisense DNA, antisense RNA, replication inhibitor, inhibitory antibodies, antibodies directed against growth factors or their receptors, bifunctional molecules comprising a growth factor and a cytotoxin,
20 bifunctional molecules comprising an antibody and a cytotoxin.

Polaxymmer 188, another antiproliferative, can also be delivered in accordance with the present invention to pave or line the walls of an artery to prevent smooth muscle growth.

- The agent delivered by the catheters and methods of the present
25 invention can also be a vasodilator, such as nitroglycerin, nitroprusside or other nitric oxide liberators. The vasodilator can also include other suitable vasoactive agents such as beta receptor blocking drugs, inhibitors of intracellular calcium transport, prostaglandins, thromboxane antagonists, and the like.

- Other cardiovascular applications can include the delivery of
30 medical grade cyanoacrylides for the treatment of aneurysms, arterial venous fistulas, or carotid cavernous fistulas. Polyvinyl alcohol products can be delivered

to treat arterial venous malformations. Papavarine, available from Eli Lilly & Co., can be delivered to treat cerebral vasospasm.

The catheters and methods of the present invention are also applicable wherever it would be desirable to deliver drugs or other agents within a lumen or vessel. For example, another procedure in which the present invention could be used is to deliver anesthesia to the prostate during treatment of benign prostate hypertrophy (BPH). The catheters and methods of the present invention can be used to deliver drugs or other agents to the urethra, bladder, rectum, bile duct, pancreatic duct and central nervous system, such as along the spinal cord, for example, as well.

The above embodiments are examples of systems and methods of the present invention, which are defined in the following claims.

Claims:

1. A catheter for delivering drugs or other agents within lumen, comprising:
an outer shaft having a lumen extending longitudinally therethrough;
an inner shaft slidably received within the lumen of the outer shaft, the inner
5 shaft having a distal portion and a proximal portion, the distal portion comprising a
plurality of grooved resilient delivery members, the delivery members having a non-
deployed position compressed by the outer shaft when the delivery members are
within the outer shaft and a deployed position when the delivery members extend
beyond the outer shaft, wherein in the deployed position the delivery members flare
10 outward beyond the outer shaft at an angle; and
the inner and outer shafts defining a space between them through which the
drug or agent is conveyed to the grooves of the delivery members.
2. The catheter of claim 1, wherein the angle is acute.
- 15 3. The catheter of claim 1, wherein the angle is essentially a right angle.
4. The catheter of claim 1, wherein the inner shaft further comprises a
guidewire lumen.
- 20 5. The catheter of claim 1, wherein the delivery members are attached to the
inner shaft.
6. The catheter of claim 5, wherein the delivery members are softer than the
25 proximal portion of the inner shaft.
7. The catheter of claim 6, wherein the proximal portion of the inner shaft is
smooth.
- 30 8. The catheter of claim 1, wherein the outer shaft comprises a proximal portion
and a distal portion, the distal portion are softer than the proximal portion.

9. The catheter of claim 1, wherein the proximal portion of the inner shaft is smooth.

10. The catheter of claim 1, wherein the distal portion further comprises a
5 grooved portion extending to and aligned with the grooves of the delivery members.

11. A catheter comprising:
an outer shaft having a lumen extending longitudinally therethrough;
an inner shaft slidably received within the lumen of the outer shaft; and
10 a plurality of grooved delivery members having distal portions coupled to the inner shaft at a first location and proximal portions coupled to the outer shaft at a second location, the first location being proximal to the second location, the delivery members having a length such that the delivery members have a non-deployed position when the first and second locations are separated by a distance
15 approximately equal to the length of the delivery members, and a deployed position when the first and second locations are separated by a distance less than the length of the delivery members, wherein the delivery members have central portions between the proximal and distal portions which extend outward beyond the outer shaft in the deployed position.

20 12. The catheter of claim 11, wherein the delivery members are moved from the first, non-deployed position to the second, deployed position by moving the inner and outer shafts with respect to each other to decrease the distance between the first and second locations.

25 13. A catheter for delivering drugs or other agents to a site within a lumen, comprising:
a delivery portion comprising a first shaft having a distal portion and at least one resilient grooved delivery member at the distal portion, wherein the delivery
30 member has a deployed position for bearing against the site and a non-deployed position for not bearing against the site;

means for deploying the delivery member from the non-deployed position to the deployed position; and

means for conveying a drug or agent through the catheter, to the delivery member.

5

14. The catheter of claim 13 wherein the means for deploying the delivery member is a thread that is tied around the delivery member in the non-deployed position and when the thread is removed, the delivery member flares outward from the first shaft at an angle with respect to a longitudinal axis of the first shaft and the
10 delivery member is in the deployed position.

FIG. 2

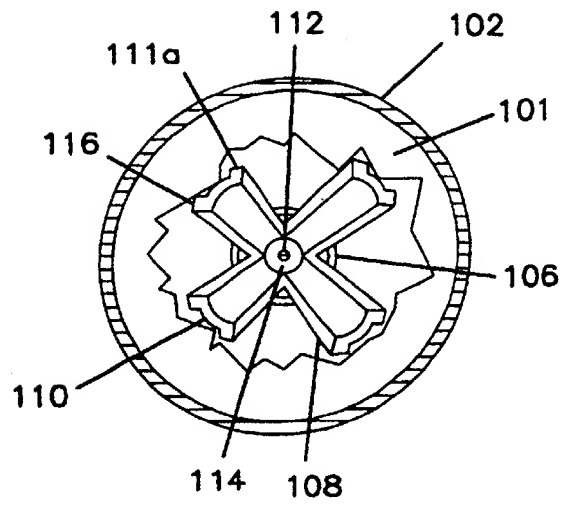
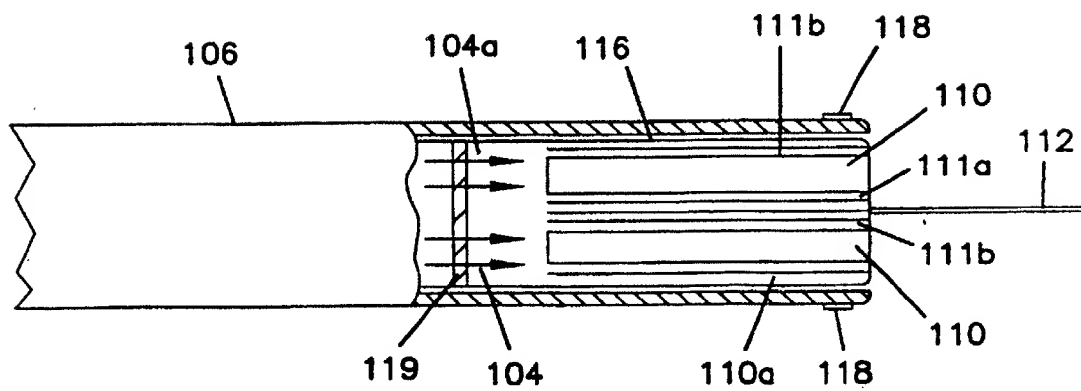


FIG. 3



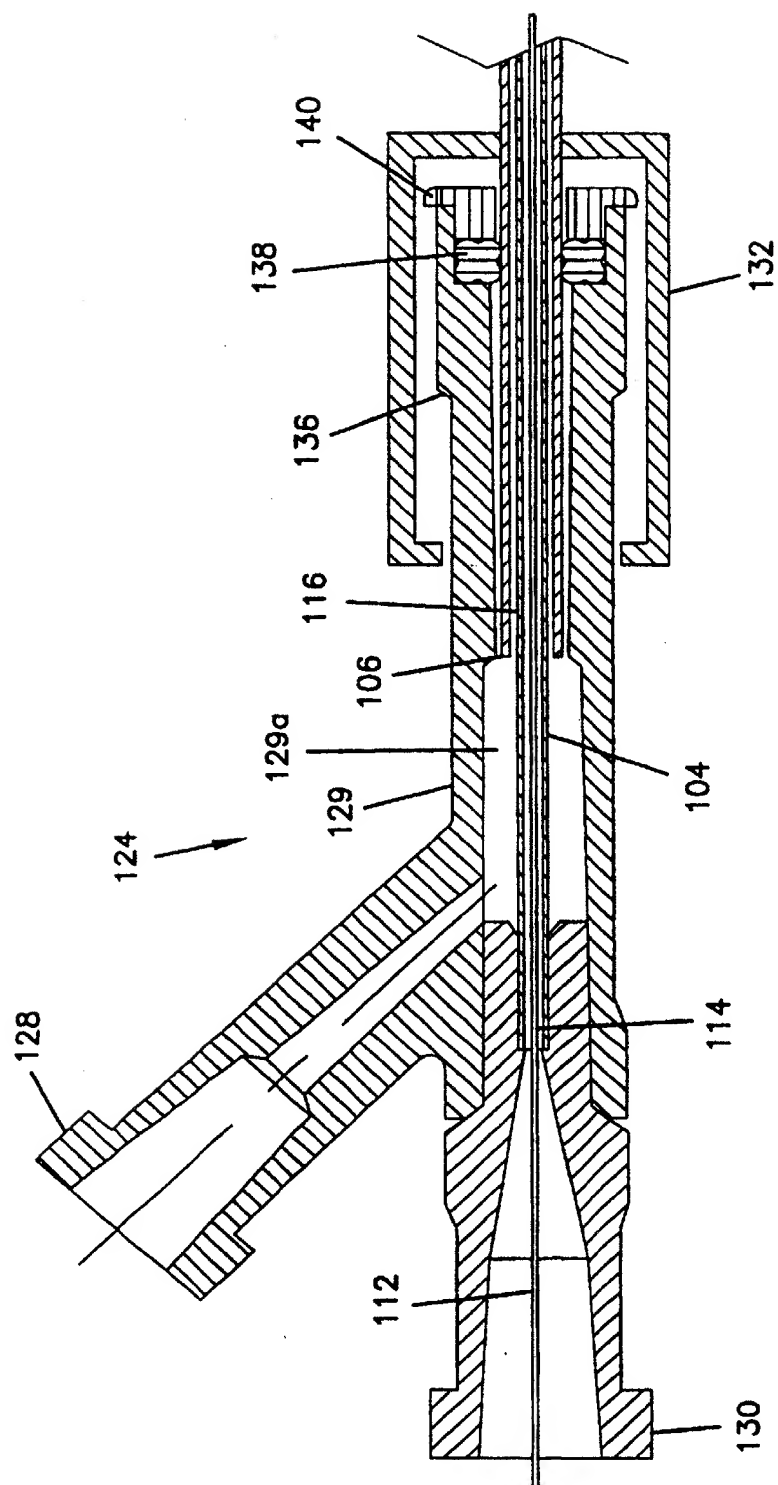


FIG. 4

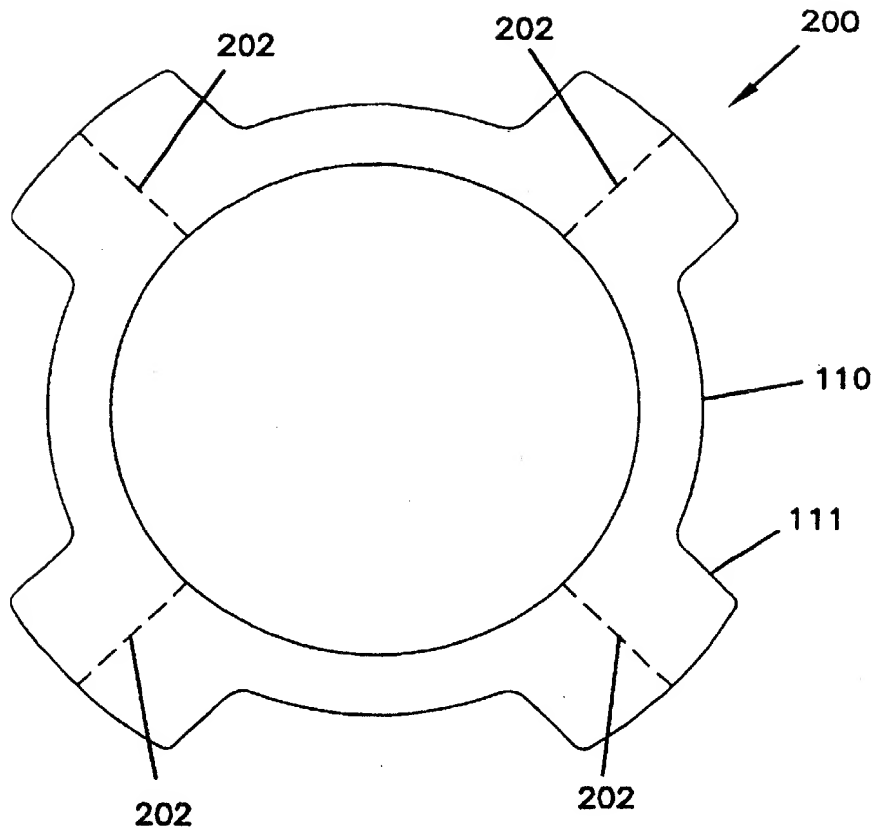


FIG. 5

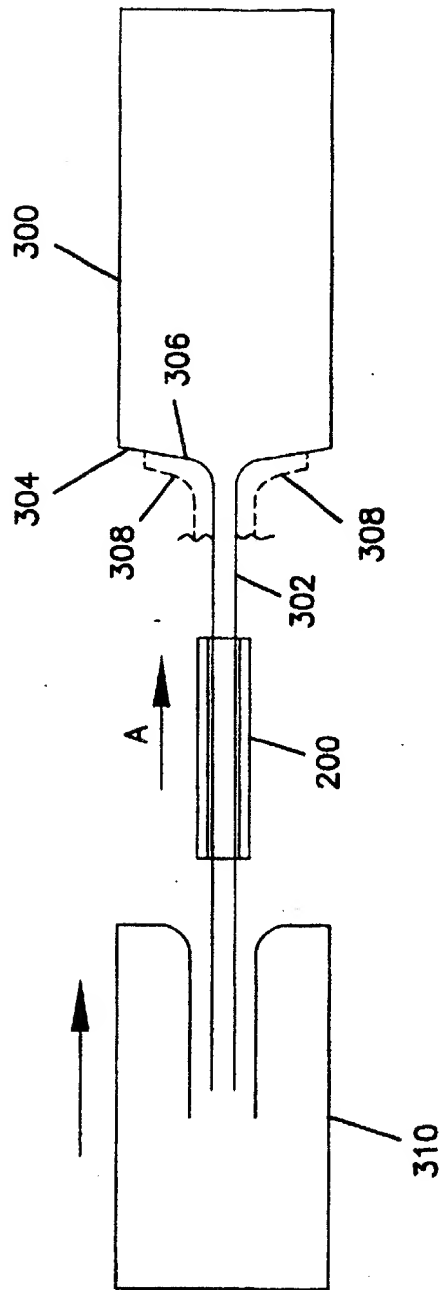


FIG. 6

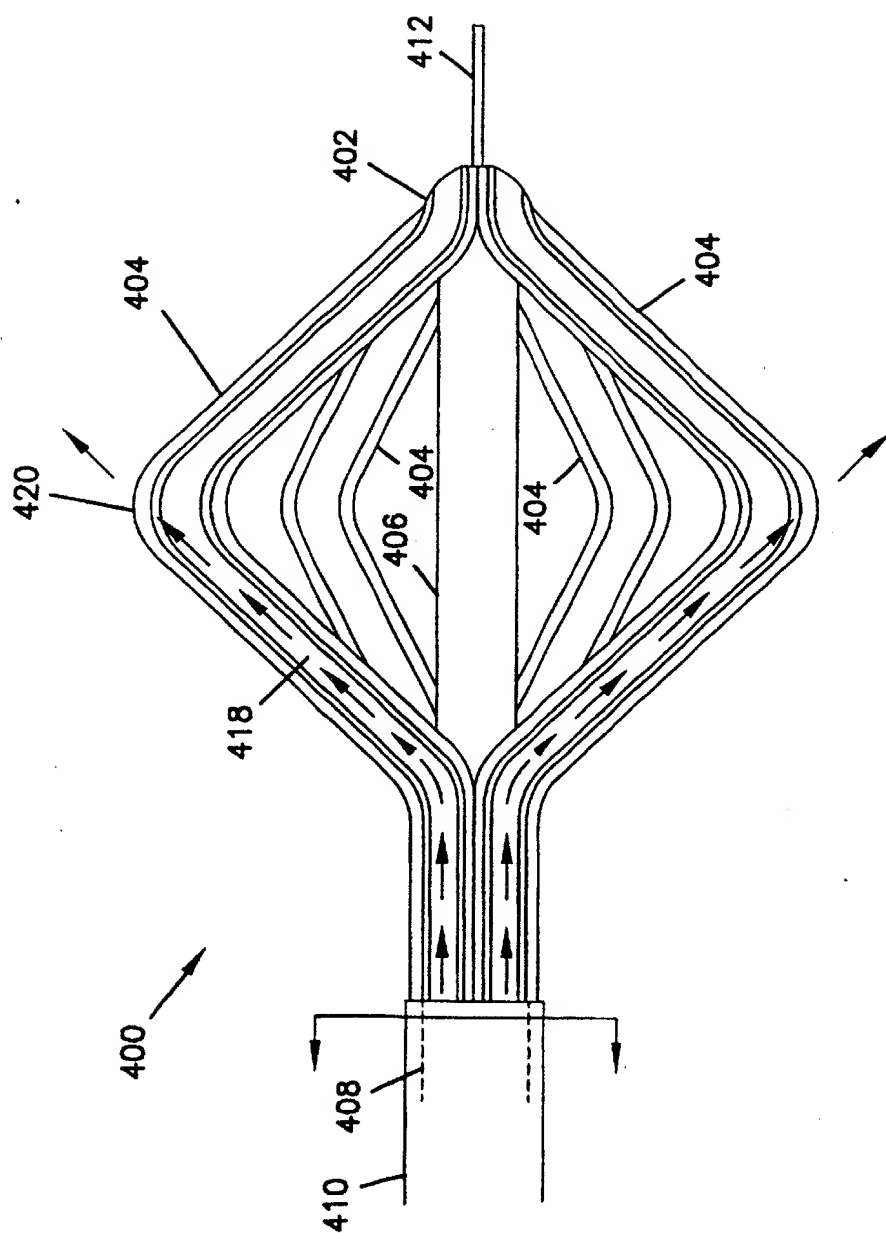


FIG. 7

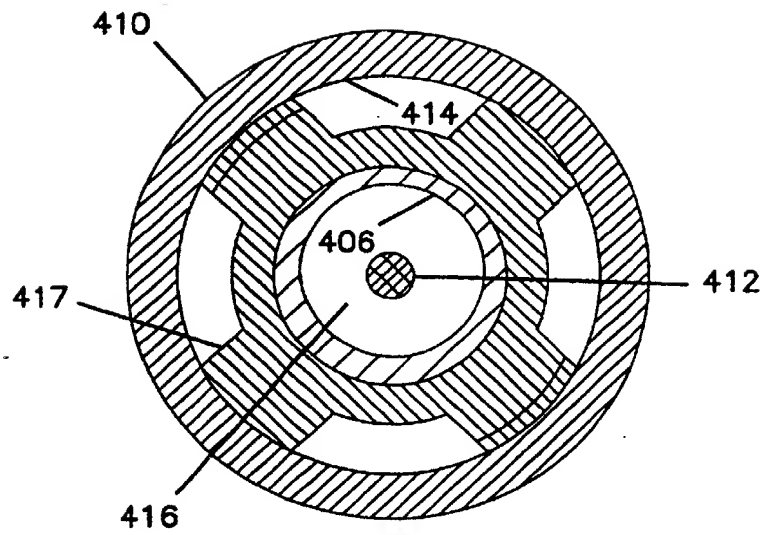


FIG. 8

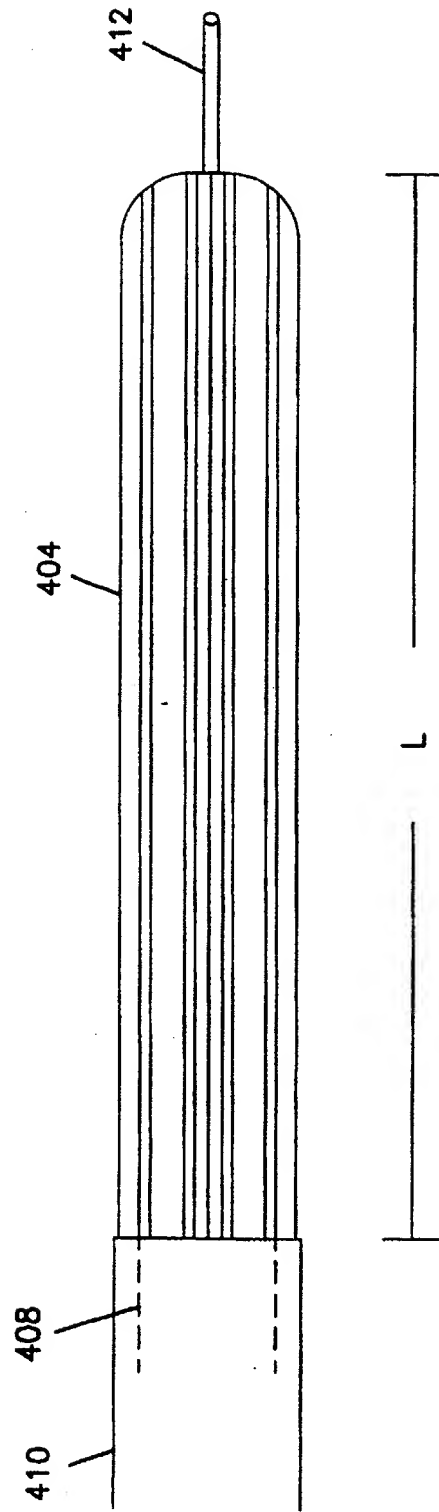


FIG. 9

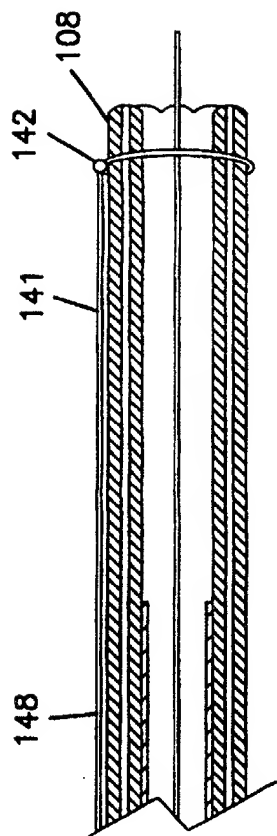


FIG. 10

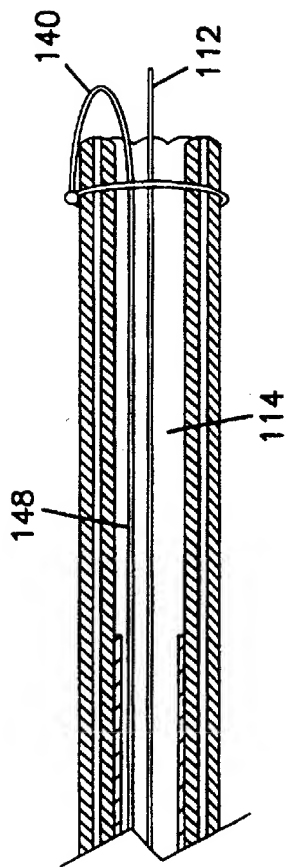


FIG. 11

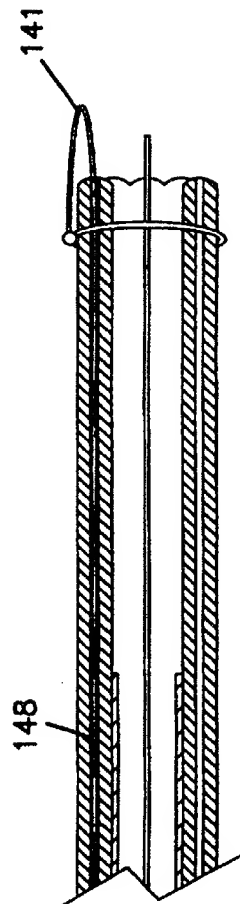


FIG. 12

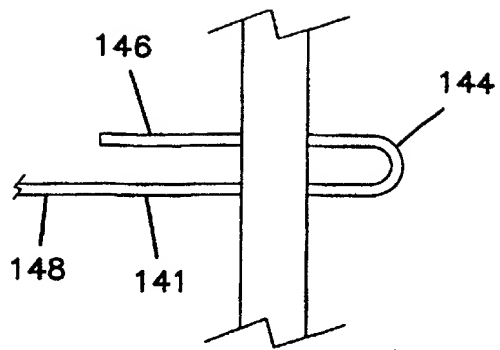


FIG. 13A

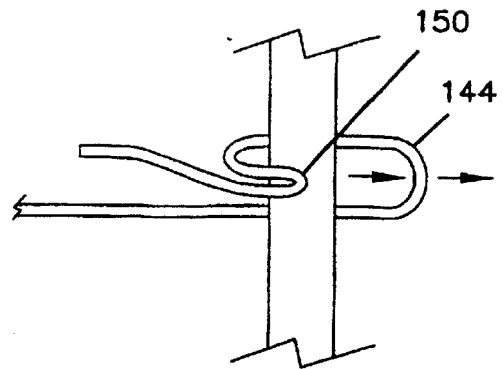


FIG. 13B

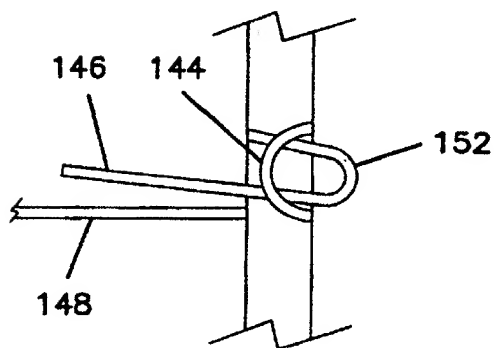


FIG. 13C

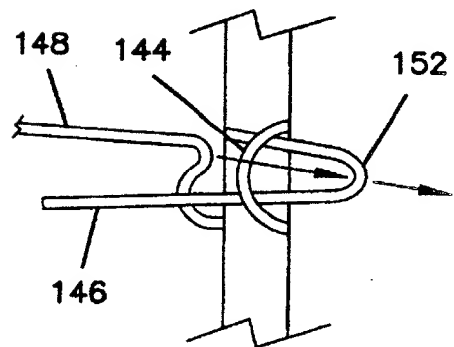


FIG. 13D

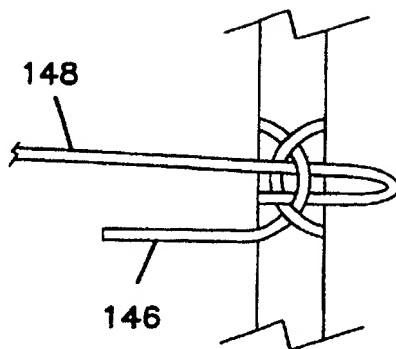


FIG. 9E

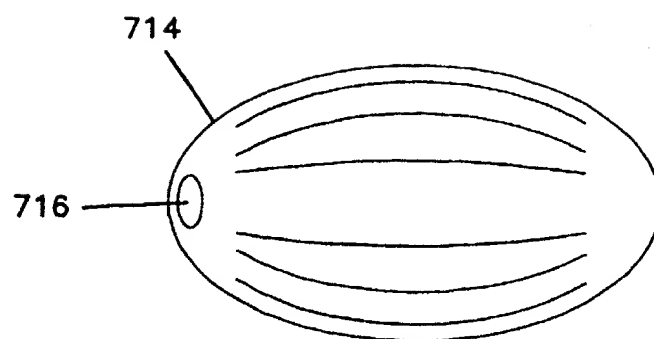


FIG. 14

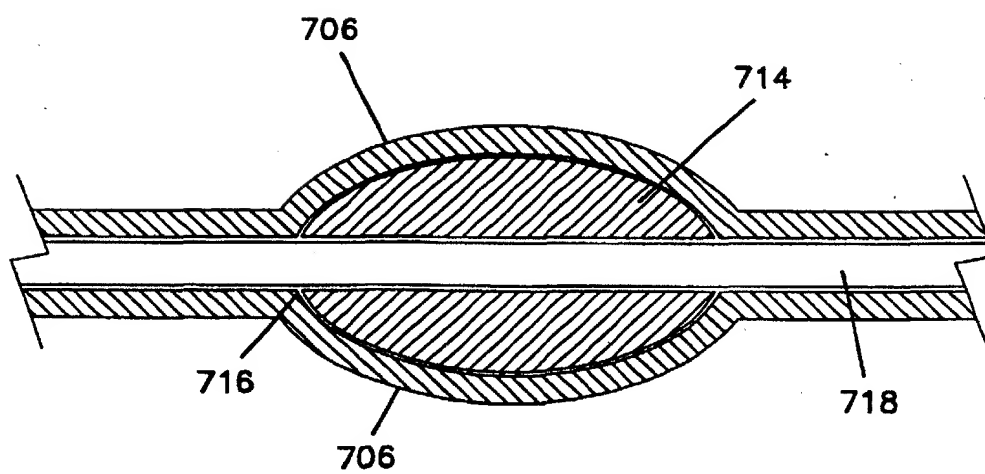


FIG. 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05487

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61M 29/00, 25/00, 5/178

US CL : 604/105, 106, 107, 164, 166, 280

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
noneElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
none

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation-of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,279,565 A (KLEIN et al) 18 January 1994, see entire document.	1-5, 8-13
A	US 3,821,956 A (GORDHAMER) 02 July 1974, see entire disclosure.	1-14
A	US 3,938,530 A (SANTOMIERI) 17 February 1976, see figures 3 and 8.	11-12
A	US 4,878,893 A (CHIN) 07 November 1989, see entire document.	1-10
A	US 5,041,093 A (CHU) 20 August 1991, see entire document.	1-14
A	US 5,267,960 A (HAYMAN et al) 07 December 1993, see figures 1-3.	1-10

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

10 JUNE 1997

Date of mailing of the international search report

11 JUL 1997

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05487

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	UA 5,306,250 A (MARCH et al) 26, April 1994, see figures 5-17.	1-14
A	US 5,318,576 A (PLASSCHE, JR et al) 07 June 1994, see entire document.	11-12
A	US 5,336,178 A (KAPLAN et al) 09 August 1994, see entire document.	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05487

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

604/105, 106, 107, 164, 166, 280, 27, 30, 48, 93, 104, 108, 109, 158-160, 264, 19;
606/191, 194, 198